

## CIK: A Path to GVL without GVHD?

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In allogeneic hematopoietic cell transplantation (HCT), the benefit of graft-versus-leukemia (GVL) effects often comes with the harm of graft-versus-host disease (GVHD). In this issue of *BBMT*, Laport et al. [1] map a possible path toward GVL with a reduced risk of GVHD.

GVL effects in humans were originally documented in observational studies by showing that the risk of recurrent malignancy was lower in patients with acute or chronic GVHD (aGVHD, cGVHD) compared with those without GVHD. Direct evidence for the potency of GVL effects came from studies showing that infusion of donor lymphocytes could induce remission in patients with recurrent or persistent malignancy after allogeneic HCT. The approach of using donor lymphocyte infusions (DLI) to treat recurrent malignancy after allogeneic HCT, however, has several limitations. First, the procedure is most effective for treatment of patients with chronic myeloid leukemia and is far less effective for treatment of other diseases. Second, the procedure is most effective when malignant cells cannot be detected and when the disease is progressing slowly, while offering little or no benefit when malignant cells can be detected or when the disease is progressing rapidly. Third, the procedure is often complicated by aGVHD or cGVHD and sometimes by marrow aplasia.

Cytokine-induced killer (CIK) cells are a heterogeneous population of immune effector cells produced by incubating blood leukocytes in medium containing interferon- $\gamma$ , interleukin-2, and an activating CD3-specific antibody for 21 to 28 days [2]. Laport et al. [1] show that under culture conditions scaled for clinical application under Good Manufacturing Practice, the number of T cells increased approximately 10-fold, and the number of natural killer (NK)-T cells expressing both CD3 and CD56 increased approxi-

mately 30-fold. Nearly all of the cells in the final product expressed CD3, and approximately half of the cells also expressed NKG2D (CD314), a cell surface molecule that functions as an activating receptor for NK cells and a costimulatory receptor for T cell activation. These CIK cells killed malignant cells through mechanisms that did not require recognition of peptide antigens presented by major histocompatibility molecules. Previous studies have shown that CIK cells have minimal cytotoxic activity against normal marrow cells or hematopoietic cells [3].

The phase I clinical trial by Laport et al. [1] was designed to assess the feasibility of using CIK cells from HLA-matched sibling donors to treat recurrent malignancy after allogeneic HCT. Using a dose-escalation design, they showed that CIK cells could be given at doses as high as  $1 \times 10^8$  per kg recipient body weight without causing acute infusion-related toxicity. Two of the 18 patients developed grade II aGVHD, and 1 developed limited cGVHD. To put these results in perspective, a previous study by Huff et al. [4] showed that approximately 40% of patients who are given conventional DLI from an HLA-identical sibling donor develop grade II-IV aGVHD or cGVHD. Results of that study did not show any apparent relationship between the number of cells infused and the risk of GVHD. Likewise, the study by Laport et al. [1] did not show a relationship between the number of cells infused and the risk of GVHD. Approximately 20% of the patients in the study by Huff et al. [4] had grade III or IV aGVHD, compared with none in the study by Laport et al. [1]. Taken together, these results suggest that the risk of GVHD is lower with infusion of CIK cells compared with conventional T cells.

Although the study by Laport et al. [1] was not designed to assess efficacy, the results showed some encouraging hints. Seven patients had measurable disease when CIK cells were infused. Subsequent complete remissions were documented in 3 of these patients, 1 with acute myeloid leukemia (AML), 1 with myeloma, and 1 with myelodysplastic syndrome (MDS). The patient with AML had been previously treated unsuccessfully with conventional DLI. The patient with AML and the patient with myeloma subsequently died with recurrent malignancy, but the patient with MDS remained alive without detectable MDS at 3 months after infusion of CIK cells. In 5 patients,

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the duration of remission after infusion of CIK cells was longer than the duration of the initial remission after HCT.

Although the available data suggest that the risk of GVHD is reduced with CIK cells compared with T cells, the efficacy of CIK cells compared with T cells in mediating GVL effects remains to be determined. Because the CIK population contained approximately 85% T cells and 15% NK-T cells, the apparent GVL activity of CIK cells could be attributed to T cells as opposed to NK-T cells. In a previous study, Introna et al. [5] observed remissions in 3 of 11 patients who were treated with infusion of CIK cells at a time when malignant cells were detectable. In each of these 3 cases, the patient had been previously treated unsuccessfully with conventional DLI. Successful remission induction by infusion of CIK cells after unsuccessful DLI suggests that the GVL activity of CIK cells was attributable to NK-T cells rather than T cells, although delayed effects of prior DLI cannot be excluded in these cases.

The low risk of GVHD demonstrated in the study by Laport et al. [1] now makes it reasonable to test whether CIK cells could be administered preemptively when the burden of malignant cells is at a nadir after HCT to prevent recurrent malignancy, especially in patients who have not previously had the benefit of a GVL effect associated with aGVHD or cGVHD. In addition, it would be of great interest to determine whether administration of NK-T cells isolated from the CIK population could decrease the risk of GVHD even further, while enhancing cytotoxic

activity against diseases that typically do not respond to conventional DLI. A final step in this possible path toward GVL without GVHD would be to decrease the complexity and costs of producing the cells, so that the approach could be exported easily to other centers.

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